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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/541,844	04/03/00	TOU J	SD-3181-00-U

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EXAMINER	
WEBER, J	
ART UNIT	**PAPER NUMBER**
1651	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/541,844	Applicant(s) TOU ET AL.	
	Examiner Jon P. Weber, Ph.D.	Art Unit 1651	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

The response with amendments filed 13 July 2001 has been received and entered. Claims 1-21 have been presented for examination.

Election/Restrictions

Applicant's election of Group I, claims 1-14 in Paper No. 6, filed 13 July 2001 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without** traverse (MPEP § 818.03(a)). Claims 15-21 have been withdrawn from consideration as being drawn to a non-elected invention.

Drawings

The drawings stand objected to because of a misspelling. Correction is required. This is **not** a requirement for **formal** drawings to be submitted at this time. As noted on the PTO 326 of 30 March 2001, applicant may not request that objections to the drawings be held in abeyance, 37 CFR 1.85(a). Failure to comply will be deemed non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for aminopeptidase from *Aeromonas proteolytica*, does not reasonably provide enablement for any *Aeromonas* aminopeptidase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The art is replete with aminopeptidases with varying specificity including one or both of: cleavage site before or after target amino acid(s), and amino acid or dipeptide is removed (see, for example Pedersen et al., US 5,783,413). It is impossible to predict *a priori* whether any given aminopeptidase isolate from any particular species of *aeromonas* will have a desired specificity. The assertion that any aminopeptidase from the genus of *Aeromonas* will be specific for cleaving an alanine residue from the amino terminus of a protein or peptide is not supported by evidence in the disclosure. The disclosure has provided a single species of organism which produces an aminopeptidase with the required specificity. Given the unpredictability of the art, a person of ordinary skill in the art would have to isolate aminopeptidase from species of *Aeromonas*, and determine its specificity without sufficient expectation of success (more likely than not). This would pose an undue burden of experimentation which is beyond mere routine.

Accordingly, the claims are not commensurate in scope with the enabling disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8 and 10-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Blumberg et al. (US 5,763,215) and Blumberg et al. (EP 191,827), only the US will be cited.

Blumberg et al. (US 5,763,215) disclose removing N-terminal amino acids from a large range of recombinantly produced polypeptides by means of the aminopeptidase from *Aeromonas proteolytica*. While most of the disclosure is directed to removing N-terminal methionine, at column 5, lines 53-57 it is stated that after the methionine is removed, the now terminal alanine can be removed from the alanine form of the natural bGH. Suitable pH values are from 7 to 10, with 9.5 being most preferred. The enzyme is said to be stable to 65°C with 37°C being most preferred. The enzyme may be bound to a solid support such as agarose or other polymeric resin, or if used in solution removed by affinity resin from the product (see columns 4-5). In the examples, the buffers used were TRIS and borate.

Claims 1-2 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Pedersen et al. (US 5,783,413).

Pedersen et al. (US 5,783,413) disclose removing amino terminal residues from recombinantly produced polypeptides and peptides by means of *Aeromonas* aminopeptidase (AAP) (the species can be gleaned from the cited EP 489,711, col. 3, lines 1-12, to be *proteolytica*). Pedersen et al. (US 5,783,413) teaches that AAP has broad specificity but is blocked by Pro and pyroGlu. Thus, claim 7 requires that Glu, Pro, Gln and Asp residues are excluded from the N-terminal when AAP is used.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blumberg et al. (US 5,763,215) and Pedersen et al. (US 5,783,413) in view of Harper et al. (US 4,900,673) and Obata et al. (JP 07,289,256) or Obata et al. (1997).

The teachings of Blumberg et al. (US 5,763,215) and Pedersen et al. (US 5,783,413) have been discussed above. Blumberg et al. (US 5,763,215) and Pedersen et al. (US 5,783,413) lack phosphate or CHES buffer.

Harper et al. (US 4,900,673) disclose using AAP to remove Met from angiogenin precursor at pH 7.2 in phosphate buffer (example 9).

Obata et al. (JP 07,289,256) or Obata et al. (1997) disclose aminopeptidase from *Aeromonas salmonicida* with high specificity for L-alanine, having a pH optimum of about 6.5 but stable from 7-10, and a temperature optimum of 45°C (see abstracts).

A person of ordinary skill in the art at the time the invention was made would have been motivated to use a phosphate or CHES buffer at a pH of about 7 because the pKa of these buffers is in this range and because Harper et al. (US 4,900,673) disclose that AAP was successfully used to remove Met from a hormone (the same reaction as mainly disclosed by Blumberg et al.) with phosphate buffer at pH 7.2. A person of ordinary skill in the art would have been motivated to use an alanine specific aminopeptidase such as that disclosed by Obata et al. (JP 07,289,256)

or Obata et al. (1997) for the expected advantage of increased specificity in the removal of an alanine amino terminal residue from recombinantly produced precursor peptides. Both Pedersen et al. and Blumberg et al. discuss the advantages of having an amino acid specific aminopeptidase remove the amino terminal residue. The selection of a particular buffer is an arbitrary matter of experimental design choice absent evidence that a particular buffer is deleterious to the enzyme activity and so long as the buffer is effective in the desired buffering range.

The broad specificity of the aminopeptidase from *Aeromonas proteolytica* was known as shown in the relied upon art and includes alanine. Several of the additional references refer to the ability of this enzyme to remove undesired amino acid residues, sometimes noting that Pro or pyroGlu block its activity. The use of this enzyme to trim recombinantly produced peptides to their final form is suggested several times. Hence, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use phosphate buffer or other aminopeptidases from *Aeromonas* species with the desired alanine specificity to trim alanines from precursor peptides.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P. Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P. Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
August 24, 2001